PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 17.08.2005
Applicant's or agent's file reference 95.80591/002	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001654	15.04.2004	15.04.2003

Applicant
ALGETA AS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hanrieder-Kreuzer, K Tel. +49 89 2399-8081

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 95.80591/002	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001654	International filing date *(day/month/year)* 15.04.2004	Priority date *(day/month/year)* 15.04.2003
International Patent Classification (IPC) or national classification and IPC A61K51/04, A61P35/00		
Applicant ALGETA AS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.11.2004	17.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Skjöldebrand, C Telephone No. +49 89 2399-8467

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001654

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-39	as originally filed

Claims, Numbers

1-20	received on 16.11.2004 with letter of 15.11.2004

Drawings, Sheets

1/1	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001654

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-13 (I.A. only)

   because:

   ☒ the said international application, or the said claims Nos. 1-13 (I.A. only) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001654

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14, 18-20
	No:	Claims	15-17
Industrial applicability (IA)	Yes:	Claims	14-20
	No:	Claims	1-13

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/GB2004/001654

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 2004/043487 A (BRACCO IMAGING SPA ; DE HAEEN CHRISTOPH (IT)) 27 May 2004 (2004-05-27)

D2: US 2001/008625 A1 (LARSEN ROY H ET AL) 19 July 2001 (2001-07-19)

D3: WO 01/60417 A (LARSEN ROY H ; ANTICANCER THERAPEUTIC INV S A (NO); HENRIKSEN GJERMUND) 23 August 2001 (2001-08-23)

D1: cf. Item VI below.

D2 discloses receptor conjugates with an antibody, a folate, and a radionuclide such as ^{227}Th (cf. claims 1-4) to be used in the treatment of different soft-tissue cancer forms (cf. claim 20). Kits where the radioligand and the antibody are separate are also described (cf. claims 22, 23).

D3 discloses conjugate systems comprising a liposome with a chelator, such as DOTA (cf. claim 3) and a heavy alpha-emitter such as ^{227}Th (cf. claim 12). The liposomes may be conjugated to antibodies and are useful in the treatment of various non-skeletal cancer forms (cf. claim 30). Kits where the liposomes, the radionuclide and the targeting molecule are in separate vials are disclosed (cf. claims 31, 32).

Novelty - Article 33(2) PCT

By the exclusion of liposomes, folate, antibodies etc. as recognition units in, novelty is

established over D2 and D3 for all the independent claims.

Inventive Step - Article 33(3) PCT

D2 and D3 are silent about the dosage of ^{227}Th. The high dosages as in the examples couldn't be derived from the prior art. Claims 1-14 and 18-20 appear to relate to inventive subject-matter.

An inventive step cannot be recognised for independent claims 15 and 17, as no dosage is referred to therein. The mere novelty-establishing exclusions of liposomes etc. are not sufficient to establish an inventive step over D2 and D3.

Industrial Applicability - Article 33(4) PCT

For the assessment of the present claims 1-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2004/043487	2004-05-27	2003-11-13	2002-11-14

D1 (WO 2004/043487) is an earlier filing (E-document) with a possible relevance for novelty in the European phase.

D1 discloses conjugates comprising ^{227}Th (claim 14) for the treatment of e.g. gastric tumours. The complexes have recognition units that appear to not belong to the excluded groups (bone-seekers, liposomes etc.). There is no disclosure on the dosage of the ^{227}Th.

D1 appears to interfere with novelty of independent claim 15.

80591002cls.doc

Claims

JC20 Rec'd PCT/PTO 12 OCT 2005

1. A method for the treatment of soft tissue disease in a mammalian subject, said method comprising administering to said subject a therapeutically effective quantity of a soft tissue targeting complex of thorium-227 and a complexing agent, wherein said quantity is such that an acceptably non-myelotoxic quantity of radium-223 is generated *in vivo* by nuclear decay of the administered thorium-227 wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments and wherein the therapeutically effective quantity of thorium-227 is at least 25 kBq/kg.

2. A method as claimed in claim 1 wherein said subject is human or canine.

3. A method as claimed in any one of claims 1 to 3 wherein said therapeutically effective quantity is at least 75 kBq of thorium-227 per kilogram bodyweight.

4. A method as claimed in any of claims 1 to 3 wherein said acceptably non-myelotoxic quantity is less than 300 kBq radium-223 per kilogram bodyweight.

5. A method as claimed in claim 4 wherein said acceptably non-myelotoxic is less than 150 kBq of radium-223 per kilogram bodyweight.

6. A method as claimed in any of claims 1 to 5 wherein said complex comprises chelated thorium-227 linked to a ligand selected from the group of antibodies, antibody constructs, antibody fragments, constructs of antibody fragments and mixtures thereof.

7. A method as claimed in any of claims 1 to 6 wherein said soft tissue disease is a malignant disease.

8. A method as claimed in claim 7 wherein the malignant disease is a disease selected from the group of carcinomas, sarcomas, myelomas, lukemias, lymphomas and mixed type cancers.

9. A method as claimed in any of claims 1 to 8 wherein said subject is also treated to combat the myelotoxicity of the radium-223 generated therein.

10. A method as claimed in claim 9 wherein said subject is provided with stem cell treatment.

11 A method for the treatment of soft tissue disease in a mammalian subject, said method comprising administering to said subject a therapeutically effective quantity of a soft tissue targeting complex of thorium-227 and a complexing agent, wherein said quantity is D_{add} as calculated from formula I below, such that an acceptably non-myelotoxic quantity D_{Ra} of radium-223 is generated *in vivo* by nuclear decay of the administered thorium-227;

$$D_{add} = \frac{D_{Ra} \times T_{Th}\left((T_{Bio})^{-1} + (T_{Th})^{-1}\right)}{1.65} \qquad (I)$$

wherein:

T_{Bio} is the biological half-life of said soft tissue targeting complex of thorium-227 and a complexing agent;

T_{Th} is the physical half-life of ^{227}Th (18.7 days);

D_{add} is the activity of the administered ^{227}Th complex (kBq/kg) and is is at least 25 kBq/kg; and

D_{Ra} is the acceptably non-myelotoxic amount of ^{223}Ra;

and further, wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

12. A method as claimed in claim 11 wherein D_{Ra} is 200 kBq/kg

13. A method as claimed in any of claims 1 to 12 in combination with at least one further treatment modality selected from surgery, external beam radiation therapy, chemotherapy, endoradionuclide therapy with radionuclides other than ^{227}Th, and/or tissue temperature adjustment.

14. A pharmaceutical composition comprising a soft tissue targeting complex of thorium-227 and a complexing agent, together with at least one pharmaceutical carrier or excipient wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments and wherein the thorium-227 is present at a therapeutically effective quantity of at least 25 kBq/kg.

15. A soft tissue targeting complex of thorium-227 and a complexing agent wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

16. A complex as claimed in claim 15 wherein thorium-227 is chelated by a derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid.

17. A method for forming a complex as claimed in claim 16 comprising heating said thorium-227 with said derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid to form a chelated thorium-227 and subsequently attaching said chelated thorium-227 to a targeting moiety.

18. A kit for use in a method as claimed in any of claims 1 to 13, said kit comprising a solution of a soft tissue targeting complex of thorium-227 and a complexing agent together with instructions for the use of said solution in said method wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

20. A kit for use in a method as claimed in any of claims 1 to 13, said kit comprising a complexing agent capable of complexing thorium ions; where said complexing agent is not a soft tissue targeting complexing agent, a soft tissue targeting compound, optionally together with a linker compound, conjugatable to said complexing agent to yield a soft tissue targeting complexing agent; and instructions for the preparation therefrom of a soft tissue targeting complex of thorium-227 and a complexing agent, and optionally also for the use of said complex in said method wherein the soft tissue targeting complex is a moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.